REMARKS

These remarks are responsive to the Office Action mailed May 8, 2009, the Advisory Action mailed August 11, 2009, and the Interview Summary mailed October 27, 2009. Claims 1, 3, 4, 6 – 16, and 22 – 28 are pending. Claims 1, 3, 4, and 6 – 16 are under consideration, and claims 22 – 28 are withdrawn as being directed to a non-elected invention.

Reconsideration and withdrawal of the rejections made in the above-referenced Office Action are respectfully requested in view of the following remarks.

Interview Summary

Applicant's representatives Arnold Turk and Walter Schlapkohl thank the Examiner for the courtesies extended to them in a telephonic interview on October 22, 2009.

During the interview, Applicant's representatives discussed the art-based rejections of the claims. In particular, Applicant's representatives pointed the Examiner to portions of the specification which distinguish the claimed subject matter from the cited art. For example, Applicant's representatives pointed to page 2, line 22 through page 3, line 17 of the specification, wherein the problems associated with the lyophilized preparations of the cited art are disclosed, including those preparations made with glycine or alanine as a stabilizer. Applicant's representatives further pointed the Examiner to Table 7 on page 24 of the specification, which summarizes unexpected results obtained by the claimed subject matter. Thus, Applicant's representatives showed how the specification distinguished the claimed subject matter from the cited art.

The Examiner indicated that he will review the specification, including the Tables, upon receipt of Applicant's written response to ascertain the showings in Applicant's Examples for the various claimed stabilizers.

Arguments as presented during the interview are present in the remarks herein.

Response to Maintaining of Restriction Requirement

The Office Action maintains the requirement for restriction with respect to claims 22 – 28, subject to rejoinder.

In response, Applicant respectfully requests reconsideration of the requirement for restriction and rejoinder of claims 22 – 28. In this regard, if the Examiner deems that any amendment to currently withdrawn claims would be beneficial, the Examiner is requested to contact the undersigned to discuss the same.

Claim Rejections – 35 U.S.C. § 103(a)

The Office Action maintains the rejection of claims 1, 3, 4, and 6 – 16 under 35 U.S.C. 103(a) as allegedly being unpatentable over Tanaka et al. (WO 97/02832; hereinafter TANAKA), in view of Yamahira et al. (U.S. Patent No. 4,244,943; hereinafter YAMAHIRA). Applicant notes that JP 9-25241, cited in the specification beginning at page 1, is a patent family member of TANAKA (see below and attachment), and refers the Office to pages 2-3 of the instant specification for a review of TANAKA's teachings as they relate to the claimed subject matter. YAMAHIRA teaches the lyophilization of urokinase using a combination of human serum albumin (HSA) with one or more polar amino acids or a salt thereof (see YAMAHIRA at Abstract).

In reply to Applicant's previous arguments, the Office Action concedes that "certain improved properties may, in fact, be present in the [instant] compositions comprising the specifically recited amino acids" (Office Action at page 4, lines 6 – 8). However, with regard to the concentration of HGF in the aqueous solution from which the claimed invention is prepared as compared to TANAKA, the Office Action asserts that "[a]bsent evidence that a product made from a higher concentration is patentably distinct, the limitation does not receive patentable weight" (Office Action at page 4, lines 23 – 24). The rejection under 35 U.S.C. § 103(a) further concludes that the claimed invention would be obvious over TANAKA in view of YAMAHIRA allegedly because YAMAHIRA indicates that many of the amino acids recited in the claims are suitable as stabilizers in compositions comprising lyophilized proteins.

In response, Applicant submits that the claimed subject matter is not obvious over TANAKA in view of YAMAHIRA. In particular, Applicant submits that the instant specification clearly distinguishes the claimed subject matter over Japanese Patent Unexamined Publication No. 9-25241, which document is a patent family member of TANAKA (see attached Esp@cenet partial listing of WO 97/02832 patent family members, including JP 9-25241 as well as US 2001/0051604, which U.S. patent application publication is relied upon by the Office as a translation of WO 97/02832). For example, Applicant submits that at page 2, line 22 through page 3, line 17 of the specification, Applicant describes the problems associated with the lyophilized preparations of JP 9-25241/TANAKA, including those preparations made with glycine or alanine as a stabilizer. In particular, the specification discloses that the use of glycine or alanine to stabilize lyophilized HGF preparations as described in JP 9-25241/TANAKA was not sufficient when HGF was lyophilized at low concentrations (specification at paragraph bridging pages 2-3, especially page 3, lines 10-14). In contrast, the claimed subject matter –

including compositions prepared from solutions containing HGF at a concentration lower than 5 mg/mL in the presence of a stabilizing agent such as arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, sodium chloride and a buffering agent – resulted in lyophilized preparations having a favorable cake forming property and extremely high stability (specification at paragraph bridging pages 3-4 and page 5, lines 10-23). Furthermore, the specification notes that the re-dissolved HGF solution taught by JP 9-25241/TANAKA had a high osmotic pressure, which causes problems of pain at administration by injection, or inflammatory rejection and hemolysis at the site of administration (specification at page 2, second full paragraph).

The specification clearly distinguishes JP 9-25241/TANAKA by way of examples as well. In particular, Test Example 4 and Tables 7 and 8 on pages 23 – 25 summarize results obtained with compositions comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, as compared to compositions which do not comprise a stabilizer or which comprise glycine or alanine as a stabilizer. In particular, Table 7 on page 24 shows that compositions comprising arginine (Example 8), lysine (Example 19), histidine (Example 20), glutamine (Example 21), proline (Example 23), glutamic acid (Example 24), or aspartic acid (Example 25) provided unexpectedly superior stability to lyophilized HGF prepared from aqueous solutions containing the HGF at a concentration lower than 5 mg/mL (e.g., 1 mg/mL). In contrast, lyophilized preparations of HGF which included no stabilizing agent (Examples 1, 4, and 28), or glycine (Examples 5 and 26) or alanine (Example 6) as the stabilizing agent, resulted in higher aggregate content after storage at 25°C, 40°C, and 50°C for one month.

In addition, as further described in Test Example 4 and Table 8 on pages 23 – 25 of the instant specification, when compositions such as those taught by JP 9-25241/TANAKA

comprising preparations from aqueous high-concentration HGF solutions (20 mg/mL) comprising glycine or alanine as stabilizers were compared to preparations from aqueous low-concentration (1 mg/mL) HGF solutions comprising glycine or alanine, it was found that aggregate formation was accelerated and storage stability was lowered in samples prepared from low-concentration HGF (see also, e.g., Examples 5 and 6 at page 12 of the specification). From these comparative experimental results it can be understood that a lower concentration of HGF gave aggregation of HGF and reduced stability even when glycine (Example 5) or alanine (Example 6) were used as a stabilizer.

Accordingly, and in contrast to the Office's assertion, evidence is present which indicates that (1) products made from a higher concentration of HGF are distinct regardless of the stabilizer utilized; (2) the compositions of the claimed subject matter are unexpectedly superior to those of TANAKA, at least insofar as addition of arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid provides considerably more stability to low-concentration HGF preparations than does addition of glycine or alanine.

At least in view of the above, Applicant submits that the Office has failed to establish a *prima facie* case of obviousness. In particular, Applicant submits that the Office has failed to show that the cited art, either alone or in combination would yield the invention as claimed. Specifically, neither TANAKA nor YAMAHIRA, either alone or in combination, teach "[a] lyophilized preparation comprising a hepatocyte growth factor, a stabilizing agent comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically acceptable salt thereof, for preventing formation of an aggregate of the hepatocyte growth factor, sodium chloride, and a buffering agent, which is prepared from an

aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL."

Based at least on the foregoing, Applicant submits that the claimed subject matter is not rendered obvious over any combination of TANAKA and YAMAHIRA. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

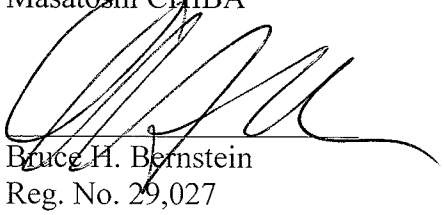
CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims. Applicant therefore respectfully requests that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

The Office is authorized to charge any required fee to Deposit Account No. 19-0089.

Should the Examiner have any questions regarding this response or this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully Submitted,
Masatoshi CHIBA



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LYOPHILIZED HGF PREPARATIONS

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- KR20050096989 (A)
- JP9025241 (A)
- ES2279522 (T3)
- DK0838221 (T3)
- DE69636953 (T2)
- CA2226548 (A1)
- CA2226548 (C)
- AU6319896 (A)
- AT355850 (T)

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Cited documents:

- JP6040935 (A)
- JP6040938 (A)
- JP6172207 (A)
- JP6247872 (A)

Abstract of **WO 9702832 (A1)**

A lyophilized HGF preparation prepared by lyophilizing an aqueous HGF solution, and a lyophilized HGF preparation further containing a stabilizer, sodium chloride, a buffer and/or a surfactant, or other additive(s). The lyophilized preparations can stabilize HGF and enables long-term storage.